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Rationale of Serum Therapy.

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AN OUTLINE OF THE PHYSICAL THEORY OF FER-
MENTATION, IMMUNITY AND INFECTION, AND
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Certain characteristics of the acute infectious diseases, as, for example, (1) the immunity that a single attack of one of these generally gives an individual to other attacks of the disease, and (2) the self-limited duration to which diseases of this class are usually limited, must have greatly puzzled physicians in the early ages of medicine, when the means of scientific investigation were meager, and the scientific data then accumulated ~~was so~~ *was* scant that inquiries into questions such as these, were in large part necessarily along the lines of a posteriori reasoning; and yet the conclusions then arrived at were often so correct that in many instances the large mass of scientific facts that have been accumulated to the present time by workers in the various departments of science, and by means of scientific aids, as mechanical devices, instruments of precision, etc., can often be placed and made intelligible only by theories of our old-time thinkers; without these old theories to orderly arrange and interpret the accumulated scientific facts, these often mystify rather than instruct us.

The vast amount of isolated, bio-chemical facts relating to bacteria, and to the toxins and tox-albumins that result from the vital action of bacteria on their food media, and the evidence that products of the action of bacteria—toxins and tox-albumins—are intimately and causatively associated with the characteristic features of the acute infections that have been mentioned,



and the remarkable phenomena of acquired immunity and of serum therapeutics, furnish an excellent example of the accumulation of knowledge of a certain kind that can not be fully utilized for the reason that the facts which have been acquired by the inductive method have outgrown their classification and interpretation by deductive theory, and also furnish an illustration wherein an old theory of fermentation, by Stahl, over 200 years ago, is better able to harmonize, unify and interpret the known facts of infection, immunity and serum therapeutics, than any yet offered, when this theory is modified by adding to Stahl's conceptions of motions in matter the knowledge that has since been acquired of this subject.

Stahl divined that fermentation and putrefaction are closely allied processes, and starting from the well known infectious nature of the latter explained both as disturbances in the molecules of the fermenting body brought about by a pre-existing molecular motion.

Liebig used this theory as the basis of a new theory of fermentation and putrefaction, which he also regarded as analogous processes. His theory attracted universal attention, and was everywhere received until it was finally overthrown by the epoch making researches of Pasteur.

Looking back upon these theories from the present standpoint, and in the light furnished by recent discoveries in molecular physics, it is seen that Stahl's knowledge, and the knowledge of his age, of motions in matter, were crude. The definite and distinctive motions in periodic time that atoms are now known to have, was unknown to Stahl; to him atomic motions were not definite and distinctive of the kind of atoms, but of the kind of motion they received from other moving bodies, hence the atomic motions of a mass would move only, and in the same manner, as they were acted upon by other atomic motions. The present belief is, that while atomic motion is definitely related to atomic heat measured from an absolute zero, and to the mass and form of the atom, it is always distinctive of the kind of atom moving;

hence the vibrations of all oxygen atoms are alike, and this is true of all other kinds of atoms.

The motions to which Liebig ascribed the changes in fermentation and putrefaction were those induced by the dissolution or disintegration of albuminous substances, which, he claimed, were imparted to, and induced like changes in, other substances with which they were in contact.

When Pasteur confirmed the results of his predecessors, and proved beyond any question that fermentation and putrefaction are caused by living micro-organisms, and are absolutely dependent on the vital activity of these, he completely overthrew Liebig's theory that these processes are caused by dead albuminous substances undergoing regressive changes, and that microbes had nothing to do with them. But when Pasteur leaves behind him the facts that he established regarding the connection between living ferments and fermentation, and enters the field of theory to explain the rationale of fermentation and putrefaction, he is no longer invulnerable; his theory is about as defective as that of Liebig's.

When the modern concepts of atomic motions are engrafted upon Stahl's theory, and this is further corrected by giving to ferments living properties that Pasteur has conclusively proved them to possess, a true basis will be furnished upon which, I think, a theory of fermentation, and the closely allied processes of putrefaction and infection, can be formed that will rationally explain all the phenomena of these processes. Now, immunity to a disease is a condition of an organism, say man, that enables him to withstand an infection; there must, therefore, be an intimate relation between infection and immunity in the underlying cause which give rise to these conditions. Likewise, the intimate causes which arrest infectious diseases, whether these operate in the natural course of the disease and give to it its self-limited duration, or whether they are produced artificially by antitoxines and arrest the progress of the disease when they are artificially introduced into the body, there must be a definite

relationship between the rationale of their action and that of the toxine of the disease they oppose.

If, now, fermentation and infection are analogous processes, that arise from similar underlying causes, as we are taught to believe by the most eminent medical teachers of the past and present ages, it must be evident that an understanding of fermentation, which is a comparatively simple process, will furnish a key that will unlock the mysteries of infection, immunity and serum therapy, that are comparatively complex phenomena. I will not ask you to accept the statements of others, however eminent, that fermentation and infection are closely allied processes, but will present some of the analogies, that you may decide for yourselves the truth of this position. They are as follows: Fermentation has for its active cause a living one called micro-organism, that constitutes the ferment; infection has for its active cause a living one called micro-organism, that is the infectious agent. Each kind of fermentation is caused by a specific ferment micro-organism; each kind of infectious disease is caused by a specific infectious micro-organism. Fermentation pursues a definite course of self-limited duration; acute infectious diseases pursue a definite course of self-limited duration. The products of fermentation will arrest the process when a definite amount of these accumulate in the fermenting solution, for example, alcohol will arrest vinous fermentation when a certain per cent of alcohol has accumulated in the solution; the products of infection will arrest the disease, and thus give it the feature of self-limitation, when a certain per cent of the products have accumulated in the system.

When the complex changes that occur in the human body by the introduction of infectious bacteria, are contrasted with the relatively simple changes that occur in a fermentable solution by the introduction of ferment bacteria, the evidence furnished by the analogies mentioned seems conclusive that the underlying causes which determine the phenomena are identical in both cases. It behooves us then to learn the nature of these causes and the rationale of their action. Beginning the investigation

with the rationale of fermentation, the most important question that is presented is, how ferments excite fermentation? Is this a chemical or is it a physical action? If it is chemical, the ferment organisms must secrete or excrete a chemical substance that induces fermentation by acting on matters contained in the ferment solution. It may be mentioned, by the way, that this view is adopted by many bacteriologists regarding those products—toxines and tox-albumins—of infectious bacteria; they are regarded as secretions of these microbes. I hold this view is altogether incorrect, and that it has caused much of the mystery that surrounds the subject of immunity. We are not left in doubt regarding the matter as it relates to fermentation; there is no longer any question that the induction of fermentation by ferment bacteria is not by chemical means, but is purely a physical process. Helmholtz, Mitscherlich and Hoffman have decided this question by a simple experiment. They found when sterilized grape juice was put into a bladder and this was immersed in fermenting grape juice that the grape juice in the bladder did not ferment. In this experiment there was a free interchange of fluids—that contained in the bladder and the fermenting solution—by osmosis, and by the same agency any soluble chemical substances contained in either solution would readily pass to the other; therefore the absence of fermentation in the grape juice contained in the bladder is conclusive against the chemical hypothesis. Other experiments, conducted by the same persons, gave the same results.

If the process is not chemical, it must be physical, and this view is strongly supported by the following facts, viz: (1) the ferments act only when in contact with the substance they ferment; (2) the products of fermentation contain in the aggregate the same elements and proportions that was contained in the ferment substance that disappeared during the process. For illustration, the alcohol, carbon dioxide, succinic acid and glycerine, that result from a vinous fermentation, contain in the aggregate the same atoms and proportions that was contained in the sugar that disappeared; the sugar is simply

transformed into these products, and there is no substance added from the ferments as there would be if the action was chemical.

What is the nature of the physical energy by which ferment bacteria induce fermentation? It is well known that bacteria are able to reduce many substances even of the most refractory nature, and that it is by this means that they break up or dissociate fermentable substances, but the *modus operandi* by which they accomplish this is not known, and it is of this power that I shall now attempt a theoretic explanation. A knowledge that bacteria are reducing agents does not alone convey information of the underlying principles they use to accomplish the work, the nature of these principles which we must understand, before we can comprehend the causes that make fermentation, infection, immunity, and serum therapeutics analogous processes. Stahl, it will be remembered, believed that fermentation is a disturbance in the molecules of the fermenting body brought about by a pre-existing molecular motion. Let us now examine this conception in the light furnished by the knowledge of molecular physics that has been acquired since Stahl's time and see if it does not furnish a basis for a rational theory. A molecule is the smallest division of a compound substance in which its properties inhere, and is a complex body composed of atoms that usually are dissimilar. An atom is the smallest known division of an elementary substance and vibrates in periods of time that are characteristic.

When now you draw a mental picture of a molecule, it will be a globular elastic body composed of many atoms that are separated from each other by a repelling force, yet drawn together by an attracting force. The various atoms of the molecule will be in active motion, each kind of atom vibrating alike, but unlike its companions. The spaces within the molecule and between the atoms will be filled with ether, that fills all space, which will be thrown into corresponding waves by the vibrating atoms. Now, ether waves, like waves in other media, are subject to interference, consequently the interatomic ether waves

within a molecule will interfere and adjust themselves so that the molecular waves are the result of atomic waves plus the effect of their interference. The amount and kind of interference that will occur between the atomic ether waves of a molecule will be determined by the manner in which the atoms within the molecule are grouped. The nature of the ether waves of a molecule will then be determined by three factors, first, the kind of atoms it contains, second, the manner in which these are grouped in the molecule, and third, the resultant of atomic ether wave interference within the molecule. All molecules are, then, surrounded by a zone of waves—molecular waves—whose nature is determined by the three factors named, and whose energy is probably in an inverse proportion to the square of their distance—characteristics that Stahl was not aware of.

The energy that molecular waves lose in size they make up in frequency, as they are believed to recur millions of times in a second. I will not attempt at this time to show that the energy of heat, light, sound and electricity is energy of wave motion; suffice it that this is not a novel conception, but an accepted truth of science. Now, the energy of waves in any medium is increased, diminished or destroyed by other like waves according as they coincide, partially coincide, or do not coincide. Illustrations of this truth will present themselves in waves of water, that are increased, diminished or destroyed by other water waves that coincide, partially coincide, or do not coincide with the first in their upward and downward motions, and in the interference in waves of sound and light. The same is true of molecular waves and is an important fact to bear in mind.

It will not be denied, of course, that all matter is molecular; ferment bacteria and fermentable substances are molecular; likewise pathogenic bacteria and the matter of the human body on which these bacteria act, are all molecular in structure; hence the war that was waged by these various bacteria on susceptible substances is a molecular war, and can best be studied from the standpoint of molecular physics. For example, the yeast cells that constitute the living vinous ferment are one-celled micro-

organisms, which are an orderly aggregation of living molecules. These molecules have energy, that is determined by the nature of the molecular waves, by which they not only dissociate sugar in the fermentable solution, but determine the molecular nature of the substance that can be formed by a chemical rearrangement of the atoms that have been dissociated; in fact, the power to determine what ferment products can be formed is a necessary result of the power of bacteria to dissociate a substance, and, what is still more remarkable, no ferment products can form that are not inhibitory to the action of the ferment. The yeast cells dissociate the sugar in the fermentable solution, because the molecular waves of the yeast coincide with those of the sugar, which, being the less stable, yields to wave impacts of the yeast which drive the sugar molecules further and further apart until, finally, they are forced beyond their chemical attractions and the sugar is destroyed. And now a remarkable phenomenon occurs. The elements of the sugar that are liberated from former attractions must again combine, *but do this under the influence of the molecular waves of the yeast ferment. This influence determines the nature of the resulting products, and none can form under this wave influence except those whose waves are inhibitory.* Alcohol, the principal product of vinous fermentation, we have seen, is inhibitory to the vinous ferment, and this but represents what is true of other ferments or pathogenic products; they are necessarily inhibitory to the causative bacteria, and this is a necessary result of the wave influence under which they are formed.

That the products of cell action inhibit the physiological function of cells, and even totally arrest this, when the products have accumulated in sufficient amounts, is a general law that applies to cell life in general, and furnishes an explanation of the benefits of therapy that is directed to "acting on the secretions."

The inhibitory action of ferment products to fermentation, and of pathogenic products—toxines and tox-albumins—to pathogenesis, have long been recognized, but the rationale of this

action has not been made known, and the cause of the self-limited duration of acute infectious diseases, the immunity that is induced by inoculations of bacterial cultures that contain the tox-albumins of the bacteria, and by what means the toxins and tox-albumins of bacteria, when gradually introduced into the tissues of a healthy animal, transform the albuminoids of its blood serum into immunizing and curative substances—anti-toxines—are questions which promise to yield up their secrets to investigation along the lines herein indicated, I will briefly outline the probable *modus operandi* by which these results are to be accomplished. The products of the vital activity of pathogenic bacteria—which are termed toxins and tox-albumins—are admitted to be the essential cause of infection when they are introduced into a susceptible organism in sufficient amount, and the cause of immunity to infection when they are inoculated, first in small doses, and then in gradually increased doses, as the system becomes tolerant. Toxins and tox-albumins are further believed to be of the nature of unorganized ferments, and to act within the susceptible organism as ferments do in fermentable solutions; that is, these toxins, by means of the energy of their molecular waves, dissociate and transform into inhibitory bodies such loosely-combined substances, within the organism, whose molecular waves make them susceptible to the molecular energy of the toxins. It will be observed that inhibitory bodies must result from the nature of this action, as they do from that of fermentation, and the cause of inhibitory power of these bodies, in the one case as in the other, is in the character of their molecular waves, which are the opposite or antagonists of the primary ferment, because of the wave influence under which ferment products are formed. The substances, say, in man's body that most probably are dissociated by pathogenic bacteria are the albuminoids of his fluids. The albuminoid molecules are massive, quite complex and have lines of weak union along which they are easily broken; besides the difference between a harmless and harmful albumen is often small and purely an arrangement of its molecules. Further-

more, there are good reasons for believing that albuminoids of the body exist in many isomeric forms; consequently the isomeric bodies would be affected differently by a species of pathogenic bacteria. One, or more, or none, of the isomers may be susceptible; if they are susceptible they would be transformed by the wave energy of the bacteria into toxins, and the subject would become infected; if none of the albumen isomers are susceptible, that is, if the molecular vibrations of none of the isomers coincide with the molecular vibrations of the bacteria, no toxin can be formed, and no infection will occur. When toxins are formed, and infection occurs, the toxins, themselves, by means of the energy of their molecular waves, produce changes in such groups of albuminoids whose molecular waves are susceptible. This action is twofold and opposite; in one case it is those albuminoid molecules whose waves oppose those of the toxin; in the other case it is those albuminoids whose molecular waves coincide with the toxin that are affected. In the first case the albuminoids that are affected are the same that are susceptible to the bacteria; that is, whose molecular waves coincide with those of the bacterium, and as the toxin of a bacterium will inhibit the molecular waves of the bacterium, it must also inhibit those albuminoids that are susceptible to the bacterium, as the molecular waves of the two are coincident.

The effect that would most likely result when the molecules of two substances, whose waves conflict, are brought together, is that the waves of the one possessed of the most energy would first overcome the waves of the weaker, and then whatever amount of wave energy that is carried over would act directly on the weaker molecules, and tend to disarrange the atomic grouping within these; that is, to convert them into other isomers, and thus render them immune to the bacterium, because the change in molecular structure of the albuminoids—that were susceptible to the wave action of the bacterium—produce a corresponding change in their susceptibilities, *i.e.*, makes them immune to this bacterium. This, I believe, is the cause of acquired immunity; those groups of albuminoid molecules

that are susceptible to the dynamic energy of the bacterium are made non-susceptible to the influence by the toxins that are formed during the progress of the disease, or that are artificially introduced into the blood.

Susceptibility of man to a pathogenic bacterium is then determined, from my standpoint, by the susceptibility of one or more groups of albuminoid molecules of the fluids of his body. Infection of the individual, or the artificial introduction of the infectious agent—toxin—destroys his susceptibility by changing the molecular structure of his susceptible albuminoids. And the permanency of acquired immunity is determined by the permanency of the changes impressed on the albuminoids by the dynamic energy of the toxin.

It will be observed that this theory requires the harmonious action of two factors before infection of an individual can occur. They are as follows: (1) pathogenic bacteria, and (2) susceptibility of one or more groups of isomeric albuminoids.

The introduction of pathogenic bacteria alone is not sufficient. Unless there are albuminoid molecules in the fluid of the body that can be transformed into the toxins of disease by the wave energy of the molecules of the bacteria, no infection will occur.

The different behavior of the pathogenic bacteria introduced into the tissues of an immune person, from the behavior of the same bacteria in a non-immune or susceptible person, has greatly puzzled bacteriologists, who have been handicapped by the prevailing theories of immunity. In immune persons pathogenic bacteria are englobed and destroyed by phagocytes, and no infection occurs; in non-immune persons, the same bacteria drive away the phagocytes and infection of the individual takes place. Now, under the prevailing opinion, that pathogenic bacteria secrete or excrete toxins, and are, therefore, always pathogenic, no rational explanation can be given why the phagocytes will destroy bacteria in one case, and be destroyed by them in the other case, but when viewed from the standpoint of the new theory the explanation is quite simple: pathogenic bacteria do not form toxins in the immune, and the phagocytes, whose function

is to destroy inert or innocuous matters in the body. destroy such bacteria as they would other innocuous matters. The case is quite different in the non-immune or susceptible individual; here there are susceptible albuminoids that the bacteria transform into toxines, which are poisonous to phagocytes, and hence the explanation of their rapid disappearance.

Why the chronic infectious diseases are not self-limited in duration, and can not be successfully vaccinated against, as the acute infectious diseases are, is another puzzling question that is simply answered by the new theory. It will be remembered that it is the loose, unstable albuminoid molecules of the fluids of the body, such as the albuminoids of the blood serum, that have their molecular structure changed by the molecular wave energy of the toxines, in the process of immunizing them. The albuminoid molecules that are susceptible in chronic infectious diseases, such as tuberculosis, lupus and actinomycosis are, on the contrary, in the fixed cellular elements, and the infective process is therefore more localized, while the molecules within the cells of fixed organized structures are less vulnerable to the wave energy of toxines, and the structures that are affected by them are limited to the immediate locality of the charge. Besides the changes that are produced in the tissues by the molecular wave energy of the toxines of chronic infectious diseases are destructive of such tissues. For these reasons tuberculin was necessarily a failure, as it rapidly destroyed tissues that had previously been weakened by the vibrations of the tubercle bacilli or of bacterio-protean, or that were quite susceptible to these vibrations. The results obtained by Pruden in his inoculations of dead tubercle bacilli, indicate that miliary tubercles may be caused by bacterio-protean; the causation of tubercles is then the result of the wave energy of tuberculin.

Of course, the condition of a person's nervous system exercises a considerable influence upon the resisting power of his albuminoids to the disturbing influence of infectious bacteria. In conditions of good health the albuminoids have more resisting power than in bad health of the person, while fear and other depress-

ing emotions render him more susceptible to infectious bacteria.

The remaining question for consideration is the explanation this theory offers of the rationale of serum therapy. Assuming that the same underlying principles control serum cures in all diseases to which this treatment is applicable, I will confine my remarks to the curative treatment of diphtheria by antitoxine, as this represents the rationale of all serum cures, and attempt an explanation of the rationale of its formation, and its action. A healthy horse is selected, and into his tissues are injected a sterilized culture of the diphtheria bacillus, beginning with very small doses, and gradually increasing the dosage until the horse finally becomes tolerant of highly lethal doses. In this condition he is poison proof to the toxine. He is now bled, and the blood serum, separated from the clot, is the agent, called antitoxine, that is used by hypodermic injection to cure diphtheria in man. The diphtheria culture that is used to render the horse poison proof is the culture liquid from which all diphtheria bacilli have been carefully removed, and it contains the diphtheria toxine in a highly concentrated condition. Of course, it is the toxine this fluid contains that gives it its potency, and it is the toxine alone that inaugurates those changes in the blood of the horse that result in the development, in this fluid, of antitoxine. Here we have another illustration of that general law to which I have referred, that the products of cell action are inhibitory, or opposing bodies. The toxine of diphtheria has the nature of a ferment, and in the blood converts all albuminoid molecules that are susceptible to its wave energy into antitoxine by virtue of the law, that the nascent atoms of a substance that has been dissociated by a ferment can not recombine under the influence of the waves of the ferment, except the combination is one whose waves inhibit those of the ferment.

The process by which toxins transform susceptible albuminoids into antitoxines is quite different from the process by which toxins render susceptible albuminoids immune. In the first instance the molecular waves of the toxine and the albuminoids are coincident—no antitoxine can be formed in the absence of such

albuminoids—and the product, antitoxine, remains only temporarily in the body. In the other instance the toxine and albuminoids concerned do not have coincident waves; on the contrary, the waves oppose each other, and those of the toxine having more energy, must first overcome those of the albuminoids before the remaining energy of the toxine can cause a rearrangement of the atomic elements of the albuminoids. Such changes do not impair the influences of the albuminoids, and they are therefore retained, and give immunity as long as the change in molecular structure persists.

In conclusion, I wish to apologize for not presenting this subject as clearly and intelligibly as I wished to, and I fear my failure to do this may prevent the reader, unless he thinks as he reads, from following the argument. The whole subject matter is so new, and is so much out of the line of argument usually pursued by medical writers, that a clear and intelligible exposition of the new theory would require more space than I can ask to occupy. Those who feel sufficiently interested in the new theory to further investigate, will find in a little volume entitled "Fermentation, Immunity and Infection," that I published in 1893, a fuller exposition of the subject.

